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16. ABSTRACT

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Regulatory History and Experimental Support of Uncertainty (Safety) Factors[1]

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A synthesis of available literature on uncertainty (safety) factors which are used to estimate acceptable daily intakes (ADIs) for toxicants is presented. This synthesis reveals reasonable qualitative biological premises, as well as specific biological data that support both the use and choice of these factors. A suggestion is made in order to derive a range of ADI. Research needs in various areas of uncertainty are also identified.

INTRODUCTION

Sensible regulation of industrial or agricultural chemicals by governmental agencies to protect public health demands that all appropriate toxicity data available on a specific chemical be used to estimate a "safe" environmental or industrial level of exposure to humans. The scientific support of such public health regulations requires a two-phased approach by toxicologists: the compilation of adequate dose–response data, usually from animal experiments, but whenever possible from available human observations, to obtain "no-effect" levels; and the assessment of these data to provide "safe" levels or to define risk levels. For a toxic chemical (i.e., noncarcinogen)[2] the "safe" level for humans is termed the acceptable daily intake (ADI).[3] Uncertainty (also called safety) factors are used extensively with human or animal toxicity data to estimate these ADIs by the general formula

[1] Although the research (or other work) described in this article has been funded wholly or in part by the United States Environmental Protection Agency, it has not been subjected to the Agency's required peer and administrative review and, therefore, does not necessarily reflect the view of the Agency and no official endorsement should be inferred.

[2] In regulatory parlance "toxicants" (i.e., noncarcinogenic chemicals) are postulated to exert their toxic effects by mechanisms which exhibit thresholds. Therefore, derivation of an ADI is appropriate. No such threshold mechanism has been universally accepted for carcinogens. Therefore, derivation of an ADI for these chemicals has not been recommended. (See text footnote 6.)

[3] An ADI is defined as the amount of toxicant in milligrams per kilogram body weight per day (or in milligrams per day for a 70-kg person) which is not anticipated to result in any adverse effects after chronic exposure to the general population of humans, including sensitive subgroups. Adverse effects are considered as functional impairment or pathological lesions which may affect the performance of the whole organism, or which reduce an organism's ability to respond to an additional challenge (U. S. EPA, 1980). Operationally, ADIs are calculated by dividing a NOEL, NOAEL, or LOAEL derived from human or animal toxicity

$$\text{ADI} = \frac{\text{"no-effect" level}}{\text{uncertainty factor}}.$$

The purpose of this paper is to present a brief regulatory history of uncertainty factors and to discuss supporting experimental observations. It is emphasized that uncertainty factors are adjustments of the NOEL, NOAEL, or LOAEL reported for small populations of humans or experimental animals in order to estimate the comparable NOAEL from chronic contaminant exposure for a large human population which includes sensitive subgroups (this level being synonymous with an ADI). However, some of these factors also incorporate a degree of safety. Other recent publications which discuss uncertainty factors are available (Calabrese, 1982; Food Safety Council, 1982). The former manuscript delves primarily into additional areas of extrapolation from experimental animals to humans; the latter review also discusses other areas pertinent to food safety.

REGULATORY HISTORY

Scientific guidelines and recommendations on the use of ADIs have been adopted by several United States governmental and international bodies such as the U. S. Environmental Protection Agency (U. S. EPA), the Food and Drug Administration (FDA), the Joint Food and Agricultural Organization/World Health Organization (FAO/WHO) Food Standards Programme (Codex Alimentarius Committee on Food Additives), and by the FAO Committee on Pesticide Residues and the WHO Expert Committee on Pesticide Residues.

Initial publications in this area of regulation appear to be by Lehman and Fitzhugh (1954) of the Food and Drug Administration. They suggested that ADIs for food additives or contaminants be derived from a chronic animal NOEL or NOAEL (measured in mg/kg of diet) by dividing by a 100-fold uncertainty factor. These authors reasoned that this factor accounted for several areas of uncertainty: intra- (human) or inter-(animal to human) species variability or intrastrain variability in response to the toxicity of a chemical, allowance for sensitive human subpopulations due to illness as compared to healthy experimental animals, and possible synergistic action of any one of the many intentional or unintentional food additives or contaminants in the human diet.

Similar areas of uncertainty have also been addressed by other authors. For example, Bigwood (1973) (associated with the WHO/FAO) justified the 100-fold uncertainty factor for food additives on the basis of differences in body size of the laboratory animal vs that of man, differences in food requirements varying with age, sex, muscular expenditure, and environmental conditions within a species, differences in water

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studies by one or more uncertainty factors. These acronyms are defined as follows. NOEL: no-observed-effect level. That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of effects between the exposed population and its appropriate control. NOAEL: no-observed-adverse-effect level. That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control. Effects are produced at this dose, but they are not considered to be adverse. LOAEL: lowest-observed-adverse-effect level. The lowest dose of chemical in a study or group of studies which produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

balance of exchange between the body and its environment among species, and differences in susceptibility to the toxic effect of a given contaminant among species. A similar approach has been adopted by the WHO Expert Committee for Pesticide Residues (Lu, 1979). Vettorazzi (1976, 1980) substantiated the use of the 100-fold uncertainty factor by discussing differences in susceptibility between animals and humans to toxicants, variations in sensitivities in the human population, the fact that the number of animals tested is small compared with the size of the human population that may be exposed, the difficulty in estimating human intake, and the possibility of synergistic action among chemicals within the human diet.

Although the specific areas of uncertainty described by these authors (Lehman and Fitzhugh, 1954; Bigwood, 1973; Vettorazzi, 1976, 1980) to support a 100-fold uncertainty factor differ somewhat, they can be generally viewed as due to intra- or interspecies variability. It has been suggested that two 10-fold uncertainty factors, one for each type of variability, be used to describe the 100-fold uncertainty factor in some instances (Bigwood, 1973; Klassen and Doull, 1980; Food Safety Council, 1982).

The FDA expanded their initial approach in the derivation of ADIs when chronic data were unavailable. In such cases where subchronic animal NOELs or NOAELs were available in two species the FDA recommended a factor of 1000 instead of 100, the additional 10-fold was ostensibly due to the added uncertainty when estimating an ADI from adequate shorter-term toxicity data (Kokoski, 1976). If subchronic data were available for only one species a 2000-fold uncertainty factor was recommended as it seemed likely that the extra margin of uncertainty would probably encompass the range of sensitivity of two species which is normally required (Shibko, 1981). The National Academy of Sciences (NAS, 1977) recommended a similar approach to uncertainty factors when estimating ADIs for pollutants in drinking water. However, the NAS recommendation differed from the FDA's in two regards: first, the NAS suggested that a NOEL or NOAEL be measured in milligrams per kilogram body weight per day versus milligrams per kilogram of diet, and second, the NAS outlined the use of a 10-fold uncertainty factor to estimate and ADI if valid experimental results from studies on prolonged ingestion by man were available. This latter idea is consistent with the general view that the 100-fold uncertainty factor is composed of two 10-fold units (*v. supra*).

The U. S. EPA (1980) recommended uncertainty factors for estimating ADIs of pollutants in ambient waters based on the NAS reasoning. The U. S. EPA also recommended an additional uncertainty factor between 1 and 10 when an ADI was estimated from a LOAEL (if a NOAEL was unavailable) in order to adjust the LOAEL into the range of a NOAEL. For example, if an ADI was calculated from an animal chronic LOAEL (other data being unavailable), an uncertainty factor of between 100 and 1000 would be recommended. Each of these latter recommendations (FDA, NAS, and U. S. EPA) were based on the 100-fold uncertainty factor, as discussed previously, when calculating an ADI from a NOEL or NOAEL found in animals.

INTRASPECIES ADJUSTMENT

Figure 1 is a plot of frequency versus an intraspecies adjustment factor obtained by raising 10 to the power (3 ÷ probit, log-dose slope) using 490 individual probit,

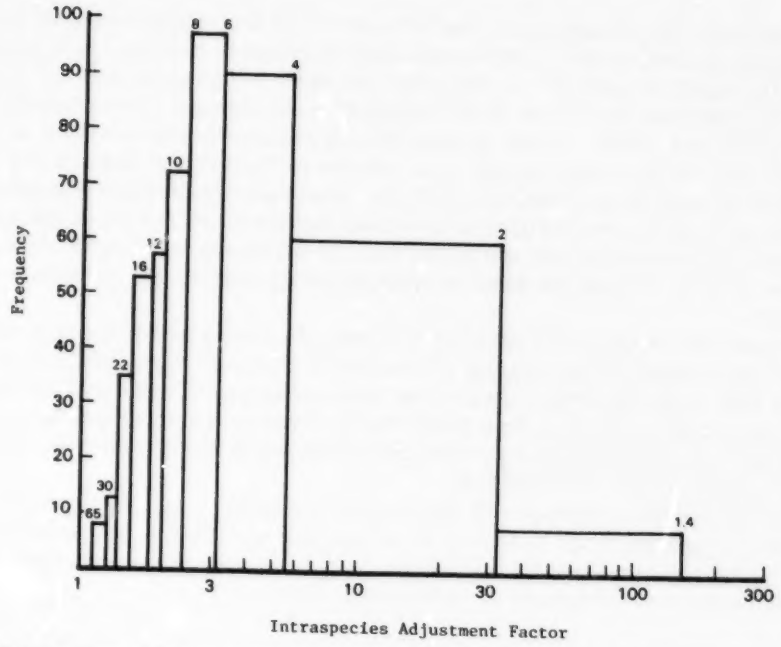

FIG. 1. Frequency vs an intraspecies adjustment factor obtained by raising 10 to the power (3 standard deviations ÷ the probit, log-dose slope). Probit, log-dose slopes are shown within the figure. Adapted from Fig. 1 (Weil, 1972).

log-dose slopes from Weil (1972). These slopes were for acute lethality and varied from approximately 1.4 to 65.

The adjustment factors of Fig. 1 can be considered as reductions in milligrams per kilogram body weight (b.w.) dose needed to scale down a median response (in this case an LD_{50}) three probits. A three-probit reduction places the median response in the general range expected for a potential sensitive subgroup of the population under study (e.g., $LD_{0.13}$). Numerical values associated with the frequencies of Fig. 1 are the slopes from Weil (1972). The most frequently occurring slopes lie within the range of 6 to 8 (97 occurrences out of 490).

Figure 1 indirectly supports[4] a 10-fold uncertainty factor to account for intraspecies variability when estimating an ADI. Approximately 92% of the probit, log-dose slopes analyzed by Weil (1972) had values of greater than 3; for these chemicals a 10-fold decrease in dose would drop a median response (e.g., an LD_{50}) below the general range expected to result in death for only the most sensitive members of this rather homogeneous population. For the remaining chemicals (i.e., those with slopes of less than 3) a 10-fold reduction in dose would not achieve this concurrent reduction in expected response.

Based on Fig. 1, a 10-fold reduction in milligrams per kilogram b.w. dose for toxicants to account for intraspecies variability when estimating an ADI at first seems

[4] The support is indirect because the endpoints (percentage mortality versus a NOEL, NOAEL, or LOAEL) are not strictly comparable.

conservative. The average probit, log-dose slope of 7.8 is associated with only a 2.4 reduction in dose to effect a three-probit drop in response. However, these probit, log-dose slopes are garnered on laboratory rats which are generally expected to be less heterogeneous in response to the toxicity of a contaminant when compared to the human population. Greater heterogeneity in response is associated with lower slopes and correspondingly greater dose reductions. Such greater heterogeneity in humans is supported by Krasovskii (1976) who claimed a 6-fold difference in sensitivity to the action of fluorine and nitrates in children, and a general 3- to 5-fold difference in sensitivity between children and adults. Thus, the intraspecies variability for humans to the toxicity of chemicals might be estimated from these data to be between 18 and 30.

Mantel and Bryan (1961) discussed this issue of probit, log-dose slopes in some detail and concluded, for purposes of extrapolation for carcinogens, that a slope of 1.0 is likely to be conservative. Such a slope would correspond to a 1000-fold reduction in dose needed to obtain a three-probit drop in response. Other authors have also discussed this issue of probit, log-dose slopes (Munro and Krewski, 1981; Oser, 1969). Their comments are addressed later.

From this brief presentation of data it seems somewhat reasonable to employ a 10-fold uncertainty factor to account for intraspecies variability in lieu of chemical-specific toxicity data. However, it is also necessary to examine this area of uncertainty experimentally or theoretically in much greater detail.

INTERSPECIES ADJUSTMENT

Figure 2 is a plot of experimental animal weight (w) versus an interspecies adjustment factor, calculated as the cube root of the assumed average human body weight (70 kg) divided by w

$$\text{i.e., } \sqrt[3]{\frac{70}{w}}.$$

These factors account for differences in milligrams per kilogram b.w. doses due to different body-surface areas between experimental animals and man, based on the assumption that different species are equally sensitive to the effects of a toxin on a dose per unit surface area. When this surface area dose is converted to corresponding units of milligrams per kilogram b.w., species with greater body weight (e.g., humans) appear to be more sensitive to the toxicity of a contaminant than species of smaller body weight (e.g., rodents). Dose conversions based on body-surface area are generally thought to more accurately reflect differences among species in several biological parameters when compared to conversions based on milligrams per kilogram b.w. (Mantel and Schneiderman, 1975). For acute toxicity to alkylating agents, equivalent doses among mammals are more accurately estimated by dose per body-surface area rather than dose per kilogram b.w. (Rall, 1969; Homan, 1972).

These factors in Fig. 2 can be thought of as reductions in experimental animal dose (in milligrams per kilogram b.w.) needed to estimate a comparable human milligram per kilogram b.w. dose. For example, a comparable milligram per kilogram b.w. dose for the average person (70 kg) estimated from a rat (0.33 kg) given an experimental dose of 100 mg/kg b.w. is 17. This human dose is derived by dividing

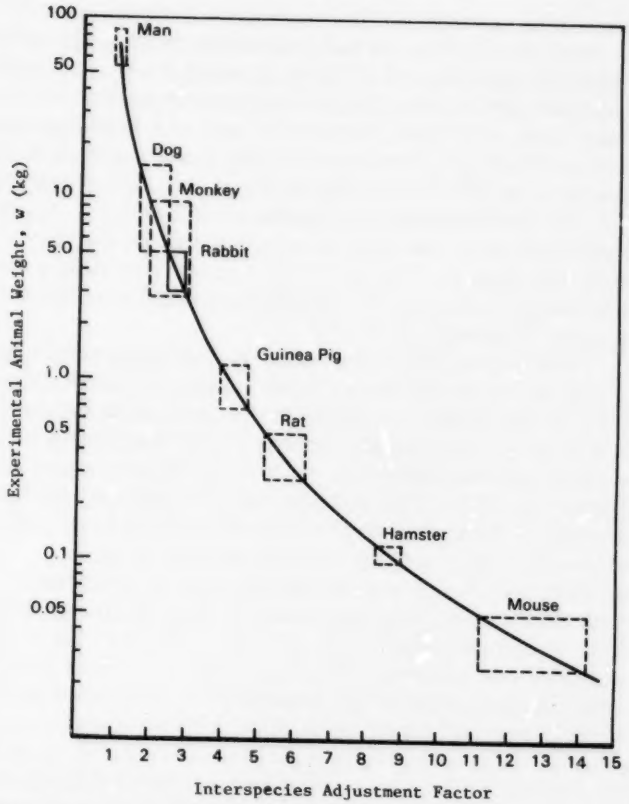

FIG. 2. Experimental animal weight (w) vs an interspecies adjustment factor calculated as the cubed root of the ratio between the assumed average human body weight (70 kg) and w. Enclosed areas along the function represent general ranges of average body weights of experimental adult animals. Rabbit values are represented by the box with solid lines. Values are from Altman and Dittmer (1962).

the animal dose, 100 mg/kg b.w., by an interspecies adjustment factor of about 6.0 (i.e., the cube root of the expression: 70 kg/0.33 kg). The enclosed areas along the function represent ranges of average adult weights for different experimental animals (Altman and Dittmer, 1962).

Figure 2 can be construed as support of a 10-fold uncertainty factor to account for interspecies variability to the toxicity of a chemical when estimating an ADI from animal doses measured in milligrams per kilogram b.w. The NAS (1977) confirms this contention by stating that man is generally more vulnerable than experimental animals on the basis of body weight by a factor between 6 and 12, but displays no supporting data. Evans *et al.* (1944) found that humans were more sensitive on a milligrams per kilogram b.w. basis than rats to a number of metallic poisons. Ratios of toxic doses between rats and humans varied between 2.5 and 152, with a geometric mean of approximately 12. Hayes (1967) compared either the smallest acute dose (milligrams per kilogram b.w.) with serious effects or the largest acute nonfatal dose for six pesticides between rats and humans. Ratios varied from 1.9 to 100 with a

geometric mean of approximately 11. Six comparisons of chronic doses which yielded similar effects varied from 0.58 to 9.4 with a geometric mean of approximately 2.9. The ratio between a 70-kg person and a 0.33-kg rat described in Fig. 2 is approximately 6.0. Evans *et al.* (1944) also described ratios of maintenance doses of vitamins between rats and humans. Such ratios varied between 2.6 and 12.9, with a geometric mean of 4.3. Lehman and Fitzhugh (1954) mention that humans were 4 or 10 times as sensitive to arsenic or fluorine in their diet as dogs or rats, respectively. These latter doses, however, were not measured in milligrams per kilogram b.w. Apparently little additional quantitative work has been done comparing the toxicity of chemicals between animals and humans, at least for the purpose of estimating safe ambient exposures. Publications in the area of estimating therapeutic doses for antineoplastic agents are available (Goldsmith *et al.*, 1975).

However, a 10-fold uncertainty factor based on these discussions to account for interspecies extrapolation appears to incorporate a margin of safety if the underlying assumption of dose equivalence among species per unit of surface area is correct. For instance, with most experimental animals a 10-fold reduction in milligrams per kilogram b.w. dose would underestimate the ADI by a factor between 1 and 10 (see Fig. 2). With mice this 10-fold dose reduction would actually predict a higher ADI. Therefore, it might be more accurate to replace this 10-fold factor with a dose adjustment between the experimental animal and man, as in Fig. 2.

In contrast, Hoel *et al.* (1975) feel that the quantitative extrapolation in the area of chronic toxic effects (ostensibly carcinogenesis) from animal to human should include both an adjustment factor based on body weight as in Fig. 2, and another factor determined by information on the contaminant and species and strain of the test animal. These authors support their suggestion by a discussion on the expected larger differences in response within the population of humans as compared to the test animal because of the heterogeneity of the human population, in addition to the differences in response among humans and animals due to different body-surface areas. However, Hoel *et al.* do not display any supporting data, and their discussion appears similar to those evoked by Lehman and Fitzhugh (1954), Bigwood (1973), or Vettorazzi (1976, 1980) for the use of a 100-fold uncertainty factor (*v. supra*). Thus, the Hoel *et al.* (1975) proposal, while perhaps reasonable for carcinogenesis, lacks specificity when estimating ADIs for toxicants. This weakness is especially evident when the available toxicity data on a contaminant are sparse.

Although data exist to support the contention that a 10-fold decrease in milligrams per kilogram b.w. animal dose is adequate to adjust to humans when chemical-specific data are not available, this area of uncertainty could profit from additional investigation.

SUBCHRONIC TO CHRONIC EXPOSURE ADJUSTMENT

Figure 3 is a plot of frequency versus ratios of subchronic to chronic exposure for either NOAELs, LOAELs, or their combination. These frequency plots are derived from a series of toxicity experiments for various compounds compiled by Weil and McCollister (1963). The subchronic exposures reported by these authors varied between 30 and 210 days; the mean value was 92 days. The chronic exposures were all 2 years. All effect levels (i.e., NOAELs or LOAELs) were determined for rats or dogs.

These experimentally determined ratios can be considered as reductions in subchronic NOELs, NOAELs, or LOAELs in order to yield the corresponding chronic

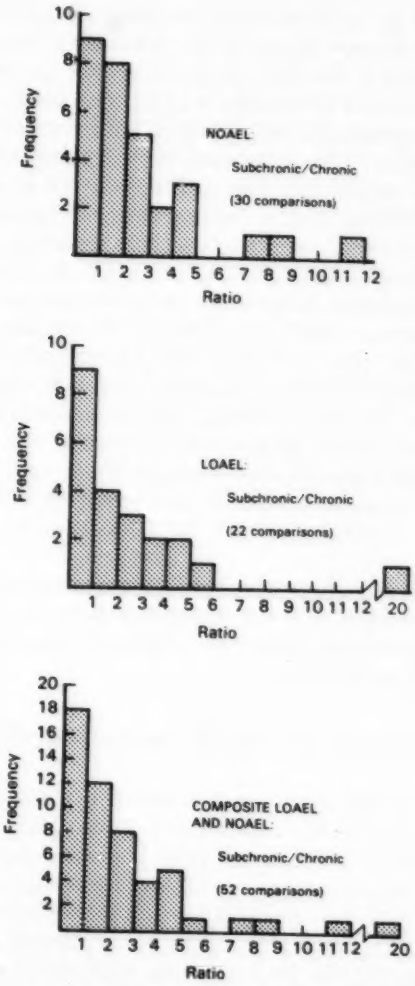

FIG. 3. Frequency vs the ratio of subchronic to chronic exposures for either NOAELs, LOAELs, or composite NOAEL–LOAEL values. Adapted from Table 1 (Weil and McCollister, 1963).

effect level. For example, a ratio of 5.0 indicates that the chronic NOAEL or LOAEL was 5-fold less than the corresponding NOAEL or LOAEL for the given chemical after subchronic exposure. It is evident from Fig. 3 that for more than half of the observed chemicals ratios are 2.0 or less. Approximately 96% of these ratios are below a value of 10.

Figure 3 supports a 10-fold uncertainty factor to account for estimating an ADI from a subchronic effect level for a chemical if a chronic level is unavailable. However, the average subchronic to chronic NOAEL or LOAEL ratio is approximately 2, which indicates that this uncertainty factor also incorporates a margin of safety. For example, if an uncertainty factor of 1000 is used to estimate an ADI from a subchronic animal

NOAEL, the ADI will be underestimated by 5-fold in over half the cases when compared to using the average ratio of 2. [An uncertainty factor of 1000 (i.e., $10_1 \times 10_2 \times 10_3$) as compared to 200 (i.e., $10_1 \times 10_2 \times 2$) in the denominator.][5]

McNamara (1976) reported the frequency of experimentally determined ratios of subchronic to chronic exposure for NOAELs on a different series of chemicals. Values of 1.0 or less were reported in 34 of 41 ratios; the remaining ratios were all less than 3.0. His compiled data suggest that dose reductions of 3.0 or less will be adequate to estimate a chronic NOAEL from a corresponding subchronic NOAEL.

The State of Michigan (1981) recommends a dose reduction of approximately 4.8 in order to adjust a mammalian subchronic NOAEL to a corresponding chronic NOAEL. This recommendation is based on a percentile-rank analysis of selected data from Weil and McCollister (1963). The NAS (1965) recommends 5% of an ADI (established by a NOAEL from a 90-day feeding study and a 100-fold uncertainty factor) as a negligible-residue level for pesticides in foodstuffs. Assuming contaminated foodstuffs will be consumed over a lifetime this recommendation can be seen as a 20-fold reduction in dose used to adjust a NOAEL observed after subchronic exposure (90 days) to that expected after chronic exposure. McNamara (1976) suggests a 10-fold reduction in dose to adjust a 3-month (subchronic) no-effect dose (NOAEL) to an expected lifetime NOAEL based on both his work and Weil and McCollister (1963).

These recommendations indicate that unless contaminant-specific data are available, it seems reasonable to employ a 10-fold uncertainty factor to account for differences between subchronic and chronic effect levels. Based on Fig. 3 such ratios are likely to be less than 10, 96% of the time.

LOAEL TO NOAEL ADJUSTMENT

Figure 4 is a plot of frequency versus ratios of LOAEL to NOAEL for either subchronic or chronic exposure, or their combination. The data for this figure are also adapted from Weil and McCollister (1963). These experimentally determined ratios can be thought of as reductions in a LOAEL found after subchronic or chronic exposure in order to yield the corresponding NOAEL. For example, a ratio of 3.0 indicates that the NOAEL found after subchronic or chronic exposure is 3-fold less than the corresponding LOAEL for a particular chemical. It is evident from Fig. 4 that all chemicals have values of 10 or less. Of these ratios 96% have values of 5 or less.

Figure 4 supports an uncertainty factor between 1 and 10 to account for estimating an ADI from a LOAEL if a NOAEL is unavailable. These data prompted Weil (1972) to suggest an additional 5-fold reduction in dose when estimating a corresponding maximum no-ill-effect level (or NOAEL) from a minimum effect level (or LOAEL). The U. S. EPA (1980) recommends that this variable uncertainty factor reflects a scientific judgment of the difference between the observed LOAEL and the hypothesized NOAEL. This difference will not necessarily be the same from experiment to experiment (as is apparent from the ratios in Fig. 4). In practice the value for this variable uncertainty factor has been chosen by the U. S. EPA (1980) from values among 1 through 10 based on the severity of the adverse effect of the LOAEL. For example,

[5] Subscripts on 10's refer to Guideline Nos. 1 through 3. See Table 1.

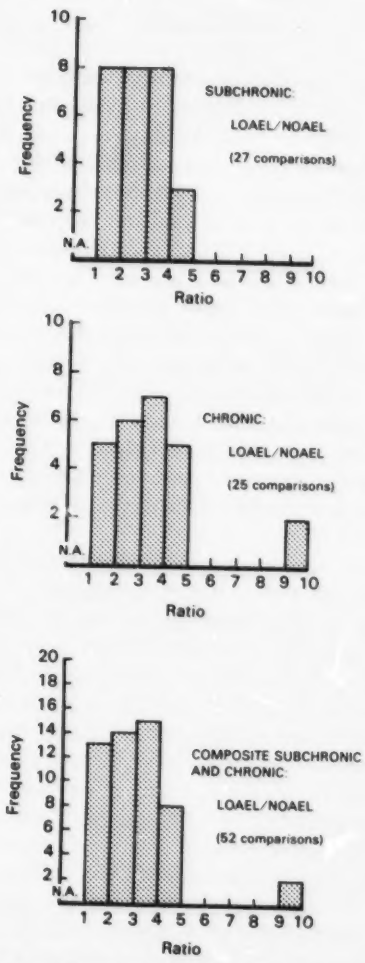

FIG. 4. Frequency vs the ratio of LOAEL to NOAEL after either subchronic, chronic, or composite subchronic and chronic exposures. A ratio of 1.0 or less is not allowable (N.A.) by definition. Adapted from Table 1 (Weil and McCollister, 1963).

if the LOAEL represents liver cell necrosis, a higher value is suggested for this uncertainty factor (perhaps 10). If the LOAEL is fatty infiltration of the liver, then a lower value is suggested (perhaps 3). The hypothesized NOAEL should be closer to the LOAEL showing less severe effects.

This concept of using variable uncertainty factors based on the severity of the observed effects if firmly established in deriving threshold limit values (TLVs) for industrial chemical exposures (Stokinger, 1972). This experience, in conjunction with the experimental data (Fig. 4) indicates that it is reasonable to employ a variable uncertainty factor between 1 and 10 when estimating an ADI from a LOAEL, in lieu of chemical-specific data.

DISCUSSION

As summarized in Table 1, several uncertainty factors are currently recommended to estimate ADIs for toxicants depending on the available human or animal toxicity data. These factors are 10, 100, or 1000 (U. S. EPA, 1980; NAS, 1977). However a perusal of the literature that discusses these factors indicates that 10, 100, and 1000 generally represent different categories resulting in multiples of 10 (i.e., 10_1, $10_1 \times 10_2$, $10_1 \times 10_2 \times 10_3$)[5] applied to the type of available data used for the extrapolation. For example, an uncertainty factor of 10 is used to estimate ADIs with appropriate chronic human data and reflects intraspecies variability to the adverse effects of a chemical (i.e., 10_1). An uncertainty factor of 100 is used to estimate ADIs with sufficient chronic animal data (supported by fragmentary human data). It accounts for both intra- and interspecies variability (i.e., $10_1 \times 10_2$). An uncertainty factor of 1000 is used to estimate ADIs with satisfactory subchronic animal data (if chronic data are unavailable). It incorporates the uncertainty in extrapolating data from subchronic to chronic exposures (i.e., 10_3), as well as the two former uncertainty factors. A variable uncertainty factor between 1 and 10 is applied to estimate ADIs using LOAELs (if NOAELs are unavailable). This uncertainty factor reduces the LOAEL into the range of a NOAEL.

In cases where data do not completely fulfill the conditions for a category of uncertainty factors (either 10, 100, or 1000), or appear to be intermediate between two categories, intermediate uncertainty factors can be used to estimate the ADI. This approach is discussed by the U. S. EPA (1980). Such intermediate uncertainty factors may be developed on a logarithmic scale (e.g., 33 being halfway between 10 and 100). This modification of the NAS (1977) approach allows scientists to judge whether, for example, dog is a more appropriate species than mouse to extrapolate to man in case of a particular chemical, and on that basis to assign an intermediate uncertainty factor instead of a uniform 10 for interspecies variability (i.e., 10_2).

Furthermore, intimate knowledge of a chemicals mechanism of toxicity, critical effect and/or pharmacokinetics in humans and experimental animals allows for the use of smaller uncertainty factors. For example, U. S. EPA (1981) suggests a 10-fold uncertainty factor to calculate an ADI for cholinesterase-inhibiting insecticides when adequate human dose–response data are available on blood cholinesterase inhibition regardless of the length of exposure. This recommendation is based on the extensive knowledge on the mechanism of toxic action and critical effect of these insecticides. U. S. EPA (1980) does not use the "no effect"/uncertainty factor approach in estimating environmental exposures when sufficient data are available on a chemical's critical effect and human pharmacokinetics. These latter procedures, however, can be used for only a few chemicals because a fairly complete data base is required.

A possible modification to the standard approach would be to present a range for the ADI rather than one value. The range could be based at the high end on the average reductions in dose needed to estimate the ADI (from Figs. 1 and 3) and the body-surface area ratio (Fig. 2), and at the low end on the standard 10-fold reductions (i.e., 10_1, 10_2, 10_3). As an example, an ADI estimated from a subchronic mouse NOAEL of 100 mg/kg/day would range from 0.10 to approximately 1.6 mg/kg/day (or 7.0 to approximately 110 mg/day for a 70-kg person). In this case the value 0.10 is equal to: 100 mg/kg/day $\div$ ($10_1 \times 10_2 \times 10_3$); whereas the higher value of 1.6 represents: 100 mg/kg/day $\div$ ($2.4 \times 13.3 \times 2.0$). In this latter calculation 2.4 is the

TABLE 1

GUIDELINES, EXPERIMENTAL SUPPORT, AND REFERENCES FOR THE USE OF UNCERTAINTY (SAFETY) FACTORS[a]

Guidelines[b]	Experimental support	References
(1) **Use a 10-fold factor when extrapolating from valid experimental results from studies on prolonged ingestion by man.** This 10-fold factor protects the sensitive members of the human population estimated from data garnered on average healthy individuals	Log-probit analysis; Log probit analysis; Composite human senstivity	Mantel and Bryan, 1961; Weil, 1972; Krasovskii, 1976
(2) **Use a 100-fold factor when extrapolating from valid results of long-term feeding studies on experimental animals with results of studies of human ingestion not available or scanty (e.g., acute exposure only).** This represents an additional 10-fold uncertainty factor in extrapolating data from the average animal to the average man.	Body-surface area dose equivalence; Toxicity comparison between humans and rats; or between humans and rats; or dogs	Rall, 1969; Evans *et al.*, 1944, and Hayes, 1967; Lehman and Fitzhugh, 1954
(3) **Use a 1000-fold factor when extrapolating from less than chronic results on experimental animals with no useful long-term or acute human data.** This represents an additional 10-fold uncertainty factor in extrapolating from less than chronic to chronic exposures.	Subchronic/chronic NOAEL comparison; Subchronic/chronic NOAEL or LOAEL comparison	McNamara, 1976; Weil and McCollister, 1963
(4) **Use an additional uncertainty factor of between 1 and 10 depending on the sensitivity of the adverse effect when deriving an ADI from a LOAEL.** This uncertainty factor drops the LOAEL into the range of a NOAEL.	LOAEL/NOAEL comparison	Weil and McCollister, 1963

[a] These factors are to be applied to the highest valid NOAEL or NOEL which does not have a valid LOAEL equal to or below it, in calculating an ADI when no indication of carcinogenicity of a chemical exists.

[b] Guidelines are in bold print. Guidelines 1 and 2 are supported by the FDA and the WHO/FAO deliberations (Lehman and Fitzhugh, 1954; Bigwood, 1973; Vettorazzi, 1976, 1980); Guidelines 1–3 have been established by the NAS (1977) and are used in a similar form by the FDA (Kokoski, 1976); Guidelines 1–4 are recommended by the U. S. EPA (1980).

reduction in dose based on the average probit, log-dose slope of 7.8 (Fig. 1), 13.3 is the mouse to human reduction in dose based on the interspecies adjustment factor in Fig. 2 (mouse weight assumed to be 0.03 kg), and 2.0 is the assumed average subchronic to chronic ratio (Fig. 3).

Uncertainty factors have generated much discussion because they have been used to estimate ADIs for toxicants whose data bases vary widely in both completeness and discrepancy. Several reports have been critical. For instance, Golberg (1975) asserts that agreement over the issue of uncertainty factors is tantamount to an admission of lack of essential information for risk assessment. Unfortunately, such lack of essential information is commonplace for many of the chemicals in our environment, and yet regulatory decisions on these chemicals are necessary.

Munro and Krewski (1981) criticize the uncertainty factor approach to human health risk estimation first on the grounds that the NOEL will depend on sample size, and second that it does not account for the slope of the dose–response curve. This latter criticism is also discussed by Oser (1969). As an example of this latter criticism, a 10-fold uncertainty factor may provide a reasonable approximation of the response in a sensitive individual if the probit, log-dose slope is 3.0, but will be conservative if the slope is steeper and not protective enough if the slope is shallower (see also previous discussion under Intraspecies Adjustment).

The first criticism is somewhat mitigated by requiring statistically or biologically significant differences (or lack of) when determining NOELs, NOAELs or LOAELs, but as Munro and Krewski (1981) indicate 0/10 and 0/100 still have different interpretations. The U. S. EPA (1980) outlines in some detail the proper choice of an effect level when faced with several, but the outline still does not completely address this first criticism.

The second criticism, that uncertainty factors do not account for the slope of the dose–response curve, raised by both Munro and Krewski (1981) and Oser (1969), has not been addressed in any systematic way. Perhaps this should not be expected. Chronic and subchronic toxicity tests are seldom conducted with a sufficient number of closely spaced doses such that a probit, log-dose slope can be determined, unless such tests are for carcinogenicity.[6] This area of uncertainty could use much additional investigation.

However, scientists associated with the WHO/FAO (Bigwood, 1973; Vettorazzi, 1976, 1980), the FDA (Lehman and Fitzhugh, 1954; Kokoski, 1976), the NAS (1977), the U. S. EPA (1980), and independent groups such as the Food Safety Council (1982) have endorsed the use of uncertainty factors. Moreover, the data discussed in this paper suggest that these factors are not arbitrary as is commonly perceived, although several of them incorporate a margin of safety that may vary.

Thus, as long as toxicant-specific human health data are meager or nonexistent, or comparable pharmacokinetic studies in humans and animals have not been conducted, uncertainty factors seem necessary for estimating ADIs of toxicants for long-term, low-level exposure. Their use in schemes for estimating acceptable intakes for

[6] Uncertainty factors have not been recommended with carcinogenesis data (U. S. EPA, 1980; NAS, 1977; Mantel and Schneiderman, 1975; State of Michigan, 1981). Weil (1972) suggested, however, the use of a 5000-fold uncertainty factor when estimating a safe level of exposure to a carcinogen from a minimum effect level (i.e., a LOAEL). This factor incorporates the standard 100-fold factor for chronic animal data (i.e., $10_1 \times 10_2$), a 5-fold factor because the extrapolation starts from a LOAEL (as discussed in the text) and an additional 10-fold factor because of the general irreversibility of the mechanisms of carcinogenesis.

exposures of shorter duration, or of multiple chemicals are also being investigated. The lack of data on chemical toxicity is even more apparent in these areas.

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